PRGF®-Endoret® Technology
BTI Implant systems

Scientific Dossier
Introduction

This scientific dossier summarises the series of indexed international articles published over the last 15 years on the range of products and technologies developed by BTI Biotechnology Institute. It highlights the vast amount of scientific evidence that backs the biosafety and effectiveness of plasma rich in growth factors (PRGF®-Endoret®) in many fields of medicine, with a particular focus on oral and maxillofacial surgery and oral implantology. This autologous technology has revolutionised the field of personalised regenerative medicine, as with the patient’s blood we can obtain different therapeutic formulations rich in growth factors, the application of which encourages healing and tissue regeneration, reducing pain and inflammation.

Many publications show the predictability and safety of BTI dental implants and of the surgical techniques (sinus elevation, split, biological drilling, etc) developed under a biological philosophy by Dr. Eduardo Anitua.

This dossier also reviews the therapeutic potential of PRGF®-Endoret® in other fields of medicine in which our research team has been a pioneer at a worldwide level: orthopaedic surgery, treatment of chronic ulcers and facial regeneration, among others.
**What are growth factors and how do they act?**

Growth factors are a set of substances that carry out an important function in intercellular communication. They carry out a large number of biological functions among which cellular proliferation is important, though they also decisively affect cellular survival, migration, differentiation and even apoptosis.

Growth factors carry out their function at very low concentrations in body fluids and tissues, in the region of pico or nanograms. They act by binding to receptors located on the cell membrane that transmit the signal from the exterior to the interior of the cell, through the coupling of different protein kinases that are phosphorylated and which regulate a signalling cascade that ends up with the activation of one or more genes.
Growth factors are a set of substances that are fundamental for communication between cells.
How can tissues be regenerated?

The process of tissue regeneration includes a complex set of biological events controlled by the action and synergy of a cocktail of growth factors. There are three agents involved in tissue regeneration: the cellular component, a combination of multiple biological mediators that include growth factors and cytokines among others and a matrix or “scaffold” that gives the new tissue under construction support.

After an injury or tissue damage, they are activated and coordinate a large number of intercellular or intracellular paths with the aim of restoring the integrity of the tissue and its hemostasis. Growth factors are also necessary to promote angiogenesis or the formation of blood vessels that will supply oxygen and nutrients to the damaged tissue. Another fundamental aspect to be considered in the regeneration of a tissue is the development of a “scaffold” that acts as a provisional extracellular matrix and therefore houses the cells as well as locally presenting the biochemical, physical and structural signals that allow the anchorage of the cellular motility machinery.
The tissue regeneration process is based on the combination of cells, growth factors and a matrix or Scaffold.
Over the last 15 years, the detailed study of platelets, of biological mediators contained in them and of the formulations aimed at allowing the administration and therapeutic use of growth factors and autologous biomaterials has allowed significant progress and has greatly increased the versatility and therapeutic possibilities of Plasma Rich in Growth Factors (PRGF®-Endoret®) technology. PRGF®-Endoret® technology is based on the preparation of platelet-rich 100% autologous plasma the application of which to damaged tissue areas speeds up the regeneration of a large number of tissues without any adverse effects.

Plasma rich in growth factors (PRGF®-Endoret®) is a personalised technology that has revolutionised the field of regenerative medicine. This article, published in one of the most prestigious journals in the field of biotechnology, summarises the most important clinical results obtained with PRGF®-Endoret®. Its application over the last decade has extended to many fields of medicine, from oral and maxillofacial surgery to dermatology, cosmetics, orthopaedic surgery and sports medicine, and more recently to ophthalmology.

How is PRGF®-Endoret® obtained?

The set of therapeutic formulations of PRGF®-Endoret® are obtained by means of a simple protocol based on a tiny volume of the patient’s blood. The blood is centrifuged (580g) in 9 ml citrated tubes during 8 minutes allowing the separation of red and white blood cells from the platelet-rich plasma. The two fractions of PRGF®-Endoret® are separated from the rest of the blood components by means of the plasma transfer device (PTD). Later, and prior to its therapeutic application, the fractions of PRGF®-Endoret® are activated with calcium chloride, leading to a series of therapeutic formulations.

The process to obtain PRGF®-Endoret® is simple and easily reproducible.

Versatility of PRGF®-Endoret®

This article, published in one of the most important scientific journals in the field of biomaterials, focuses on the enormous versatility that PRGF®-Endoret® technology offers, as by using the patient’s blood we can obtain up to 4 biocompatible formulations:

a. PRGF®-Endoret® supernatant: used to cultivate primary cells and stem cells in the laboratory, it is also the base of a new collyrium for treating a large number of pathologies of the ocular surface.

b. Liquid PRGF®-Endoret®: Ideal for infiltrations in skin, musculoskeletal system tissues, TMJ, etc. It is the perfect tool to bioactivate dental implants and prostheses of all types with the aim of accelerating their osseointegration.

c. PRGF®-Endoret® clot or “scaffold”: Ideal to fill in defects and promote tissue regeneration: post-extraction, treatment of ulcers, tissue engineering, etc.

d. Fibrin membrane: due to its hemostatic properties it is the best biomaterial to seal defects and stimulate epithelisation.
The versatility of PRGF®-Endoret® technology allows you to obtain up to 4 autologous formulations.
Why does PRGF®-Endoret® work?

The biological activity of the different formulations obtained with PRGF®-Endoret® technology is based on two fundamental pillars. On the one hand, the content in plasma and in particular platelet growth factors whose action regulates the main processes involved in tissue regeneration.

On the other, the fibrin matrix, which is used as a provisional structure to house the cells and control the release kinetics of the growth factors present in PRGF®-Endoret®.

This article published in the prestigious journal Trends in Pharmacological Science, the most important in the field of pharmacology, talks about the therapeutic potential of PRGF®-Endoret® technology and in particular describes how the perfect synergy between growth factors and fibrin is a key aspect when explaining the clinical results obtained with this autologous technology.

What makes PRGF®-Endoret® different to other platelet-rich plasmas?

PRGF®-Endoret® is the first 100% autologous platelet-rich plasma to be described in literature worldwide. It is, likewise, a pioneering technology in translational regenerative medicine. Over 15 years of research, added to its exclusive properties, make PRGF®-Endoret® a unique technique. PRGF®-Endoret® is prepared with small volumes of the patient’s blood and does not require the use of thrombin or chemical agents for its activation. Unlike other products, it does not include white blood cells (leukocytes) in its composition, which gives it more effective anti-inflammatory properties. It is the most versatile technology, as its multiple formulations offer a large number of therapeutic applications. In short, as shown by the series of letters to the editor published during recent years, we can define PRGF®-Endoret® as a platelet-rich autologous plasma whose effectiveness and safety have been widely proven. However, it is important to remember that not all platelet-rich plasmas are PRGF®-Endoret®.

DEMONSTRATION VIDEO
Scan this code with your mobile phone to watch the video.


The pillars of PRGF®-Endoret®: growth factors

PRGF®-Endoret® contains a cocktail of autologous growth factors that proceed from both the plasma and the platelets. In fact, the platelets have a complex storage system in the form of intracellular granules that allow them to transport a large number of biologically active molecules. According to some authors, this list of proteins and peptides can come close to 500 molecules. Alpha (α) granules are the most abundant as there are around 40 to 80 alpha granules per platelet, but they are also the ones with the greatest retention capacity. In addition, they contain a series of antibacterial proteins that are generically called thrombocidines and which are lethal for a large variety of bacterial species.

However, it is important to remember that the plasma contains important growth factors and that the combination of the plasma and platelet factors is a key element in the biological action of PRGF®-Endoret®.

El PRGF®-Endoret® contains hundreds of molecules including plasma and platelet growth factors.
Platelets release substances that promote tissue regeneration and which modulate both angiogenesis and inflammation. Important among other factors we have PDGF: platelet-derived growth factor, TGF-β: transforming growth factor β, bFGF: basic fibroblast growth factor, VEGF: vascular endothelial growth factor, EGF: epidermal growth factor or angiopoietin-1 among others. They release in parallel antibacterial molecules and specific growth factors that act on the mobilisation of progenitor cells from the bone marrow or from peripheral niches.
Platelets release growth factors responsible for coordinating the regenerative tissue response.
Calcium acts as a cofactor in the activation process of PRGF®-Endoret®, which allows the conversion of the fibrinogen of the plasma into fibrin, generating a gel or clot with important biological functions. On the one hand, fibrin is an excellent matrix to maintain and house the cells, it acts as a provisional scaffold while the definitive tissue is regenerated and acts as a continuous growth factor release system. It is therefore a biocompatible and autologous sponge full of growth factors and cytokines that will permit a progressive release of them during several weeks.

The fibrin obtained with PRGF®-Endoret® technology is probably the best biomaterial for encouraging tissue regeneration.
In over a decade of preclinical research, during which tens of cellular phenotypes were studied, we have managed to discover and understand the multiple biological functions that the set of therapeutic formulations of PRGF®-Endoret® carry out. The biological mediators of PRGF®-Endoret® stimulate and encourage such important processes for tissue regeneration as cellular proliferation and migration, chemotaxis (or the call from a distance for cells to go to the location of the injury), inflammation and the auto/paracrine synthesis of new molecules with biological activity.


The growing interest in the range of biological options that PRGF®-Endoret® offers has even reached the field of stem cells. Stem or progenitor cells are characterised on the one hand by their unlimited capacity for proliferation, and on the other by the possibility of undergoing asymmetrical division (that is, self-renovation) maintaining their stemness while at the same time they can differentiate to diverse types of cells. There are different types of stem cells depending on their origin and their anatomical location.

There is evidence that the content of biologically active agents in PRGF®-Endoret® affects the mobilisation, adhesion, proliferation, survival, activation and differentiation of mesenchymal stem cells and other subtypes of precursor cells.

In addition, the cocktail of growth factors of PRGF®-Endoret® is an ideal resource for the cultivation and expansion of stem cells in the laboratory.


Mechanism of action of PRGF®-Endoret®

The use of growth factors and autologous fibrin for regenerative purposes represents a new approach to personalised medicine that a large number of patients could benefit from. In this paper, published in one of the most important journals of drug delivery, they discuss the mechanisms of action through which PRGF®-Endoret® produces its multiple therapeutic effects.

The stimulation of cell proliferation and migration along with the call to circulating cells to come to the location of the injury are basic aspects of the action of PRGF®-Endoret®.

Likewise, also important is the angiogenic action of the growth factors which is crucial to start regeneration. Last of all, though no less important, its anti-inflammatory and antibacterial properties are a key element.
Our research team has proven that PRGF®-Endoret® presents bacteriostatic activity with a large number of bacterial and fungal strains. This is because the platelets contain a series of antibacterial proteins called thrombocidines. These proteins are part of a wider family known as defensins, and they are of a cationic nature, which will allow them to bind to and alter bacterial membranes. In addition to thrombocidines, platelets transport and release other antimicrobial peptides among which we should mention platelet factor 4, RANTES, tissue activating peptide 3, the basic protein of platelets, thymosin β-4, and fibrinopeptides A and B.

In a recent paper we could see that the bacteriostatic potential of platelet-rich growth factors is due both to the antimicrobial peptides and to the fibrin, and not to the presence of leukocytes in their composition. In fact, the bacteriostatic effect of PRGF®-Endoret® is identical to that of a platelet and leukocyte-rich plasma. Another important conclusion of this study was to confirm how the inclusion of leukocytes notably alters the structure and uniformity of the fibrin matrix.
PRGF®-Endoret® presents bacteriostatic activity with a variety of bacterial strains.
This dossier summarises the preclinical and clinical scientific articles that endorse the biosafety and efficacy of PRGF®-Endoret® in many fields of medicine.


This revision article is a reference in international bibliography as it is the journal with the greatest scientific impact. It is about the therapeutic potential of platelet-rich plasma, and in this specific case, PRGF®-Endoret®.

The use of growth factors and autologous fibrin for regenerative purposes represents a new approach to personalised medicine that a large number of patients could benefit from.
Field of Oral Surgery

Introduction

The versatility of PRGF*-Endoret* has allowed its use in the treatment of a wide range of clinical problems within the field of oral and maxillofacial surgery. An example of this is the following series of applications developed by our research team over the last two decades and summarised in the scientific dossier. From the treatment of the alveolus post-extraction to the use of this technology in gingival recessions or in the humectation of dental implants to encourage their osseointegration, the range of therapeutic possibilities is enormous. The possibility that PRGF*-Endoret* offers of working with a liquid formulation, with a three-dimensional matrix or a with retracted fibrin membrane drastically increases the number of therapeutic options and applications. We must not forget that thanks to its agglutinant properties, PRGF*-Endoret* technology is the “perfect fellow traveller” to prepare grafts, whether they are autologous bone, allogenic or any other biomaterial for bone regeneration.
In the late 90s Dr. Anitua developed a pioneering technique to humectate implants and bioactivate their surface with fibrin and autologous growth factors. In a simple procedure, the implants are soaked in freshly activated liquid PRGF-Endoret and in this way a fibrin membrane full of growth factors is generated that will encourage a faster osseointegration of the implants.

The nano-rough surface of BTI implants is specially designed to boost the biological effects of PRGF®-Endoret®.
In this study carried out with research animals the aim was to determine whether the humectation of the implant surfaces with PRGF®-Endoret® encouraged their osseointegration. To this end a total of 23 implants were inserted in the tibia/radius of 3 goats; 13 of them were previously humectated with PRGF®-Endoret® while the other 10 were not (control). 8 weeks later, a histomorphometric analysis was carried out on the bone biopsies of the sacrificed animals and we observed that the value of the bone-implant contact (BIC) was 51.28% in the animals humectated with PRGF®-Endoret®, as opposed to 21.89% in the implants that were not humectated, generating a significantly greater area in the former (p<0.01).

These results prove how the humectation of implants with PRGF®-Endoret® encourages their faster osseointegration.
Humectation of BTI implants with PRGF®-Endoret® encourages faster osseointegration.
This new study carried out on research animals evaluated the effect of humectation of dental implants with PRGF®-Endoret® to encourage and accelerate their osseointegration. To this end 2 dogs were used in which 12 implants were inserted, 6 on each side of the mandible, humectating the implants of one side with PRGF®-Endoret®, and placing the implants of the opposite side without humectation (control). After 12 weeks, the implants were extracted along with the adjacent bone for a histological-histomorphometric analysis. The results showed that the implants humectated with PRGF®-Endoret® presented higher levels of BIC (bone-implant contact). We also observed higher values of trabecular bone thickness and bone maturity in the areas treated with PRGF®-Endoret®.

The aim of this study was to assess both the morphology and the composition of the interface formed by the implants activated with PRGF®-Endoret®. Both features are of capital importance for later regenerative events as both the morphology and the composition of the interface allow the modulation, among other aspects, of the balance between inflammation and regeneration around the implant. In this article we could see through electron, atomic and confocal microscopy that the bioactivation of implants with PRGF®-Endoret® generates a three-dimensional scaffold with a multitude of platelets, proteins and growth factors. In addition, the composition of the interface of the surfaces bioactivated with PRGF®-Endoret® is specific, containing platelet and protein elements different to those of other surfaces assessed. The specificity of both the morphology and the composition of the interfaces formed with implants bioactivated with PRGF®-Endoret® is very possibly the reason behind its beneficial clinical results.

The biological potential of PRGF®-Endoret®

Preclinical Research

In this laboratory test we analysed whether the new fraction F2 of PRGF®-Endoret® produces the same biological effect as the old fraction F3. To this end the potential was evaluated of the different formulations of PRGF®-Endoret® in the stimulation of different biological processes in human gingival fibroblasts, including the proliferation, migration and adhesión of fibroblasts, as well as the autocrine release of some angiogenic factors and components of the cellular matrix. The results observed showed that PRGF®-Endoret® significantly increased the cellular proliferation, migration and adhesion of gingival fibroblasts. These results showed how PRGF®-Endoret® is capable of promoting the regeneration of gingival connective tissue and highlighted the biological potential of the new fraction F2 of PRGF®-Endoret®.
In another study carried out on human osteoblasts, again we saw the biological potential of the new fraction F2 of PRGF®-Endoret® and it was compared to the previous one, F3. To do so we evaluated: proliferation, migration, chemotaxis, autocrine secretion of growth factors and the production of components of the extracellular matrix. The results showed that the new F2 managed to increase the proliferation, migration and chemotaxis of the osteoblasts. In addition, the autocrine expression of two relevant pro-angiogenic factors: VEGF and HGF was significantly improved, and that of three osteoblastic activity markers: procollagen I (PC), osteocalcin (OC) and alkaline phosphatase (ALP). These results showed how the new fraction F2 of PRGF®-Endoret® stimulates some of the biological processes of the main cells responsible for bone regeneration and its effects are biologically comparable to the previous one, F3.

Biomechanical Studies

Preclinical Research

This biomechanical study was carried out with the aim of evaluating the influence of straight alignment versus distal offset on the bone stress distribution that the bone around the implant sustains. A mesial load of 200 N and a distal load of 230 N were applied to the prosthesis. These results showed that the fact that there is a limited offset (of up to 2.5 mm) of the prosthesis on the implant does not increase stress on the adjacent bone.

A controlled offsetting of the implant on the prosthesis, in addition to allowing an optimal aesthetic restoration and reducing the emergence profile, does not increase bone stress and a possible risk of implant failure.

The use of larger diameter implants will reduce even further the stress in the bone adjacent to the implant.

The aim of another biomechanical study was to evaluate the influence of the length, diameter and geometry of BTI implants on bone stress distribution. 3D finite element models were created and a load of 150 N was applied at an angle of 30 degrees. Different diameters (3.5 to 5.0 mm) and lengths (8.5 to 15 mm) were evaluated. The results showed that the effect of the implant diameter on bone stress distribution was more significant than the effect of the length or geometry. On the other hand the maximum stress was located around the implant neck and most of it in the bone adjacent to the first implant threads. According to the results observed, the use of greater diameter implants can be beneficial to reduce stress around the implant, meaning that the use of short implants with a greater diameter could be a reasonable alternative in locations where residual bone height is limited.

After the extraction of a tooth a healing and regeneration process starts for the tissues involved that will affect the final volume of alveolar bone and the structure of the ridge. An excessively traumatic extraction or an insufficient regeneration can lead to an excessive loss of bone tissue, a delay in the replacement of lost teeth with implants, may require invasive reconstruction techniques, or may generate a permanent defect without any possible correction.

In order to modify this process favourably and to promote adequate regeneration, there are different therapeutic tools among which we could mention those aimed at isolating the defect and preventing the growth of conjunctive tissue towards its interior (membranes), materials susceptible of filling in the defect and substances with osteogenic and osteoconductor properties such as PRGF®-Endoret®.
The PRGF®-Endoret® clot is ideal for filling in the alveolus post-extraction and for releasing growth factors that promote its regeneration.
This article is the first in scientific literature that describes the use of 100% autologous platelet-rich plasma in oral and maxillofacial surgery. The aim of this pioneering study was to evaluate the use of PRGF-Endoret® in the regeneration of alveoluses post-extraction. To carry it out 20 patients were included who were randomly given PRGF-Endoret® or the traditional treatment with suture. Biopsies were collected from 6 to 10 weeks after the extraction.

The results showed that epithelisation was very good or excellent in the cases treated with PRGF-Endoret® and normal in the control group. Regeneration was practically complete in 8 of the 10 cases. The biopsies of the areas treated with PRGF-Endoret® showed mature compact bone with well organised trabeculae and normal morphology. In all the biopsies of the control group there was only connective tissue containing bone trabeculae, but in no cases mature bone. The results were significantly better when PRGF-Endoret® was used and no adverse effects were observed.

This clinical study was focused on evaluating the clinical results of implants placed immediately in post-extraction sites using PRGF®-Endoret® as an adjuvant during surgery. A total of 30 patients were included in the study with chronic periapical lesions that required an extraction and a total of 61 implants were placed. Survival and bone loss were assessed 1 year after the implants were placed. The results after an average follow-up period of 18.5 months showed a survival rate of 98.4%. Average bone loss was 0.41 mm.

These results prove that the use of PRGF®-Endoret® for the immediate placement of implants in alveoluses post-extraction can be considered an effective, safe and predictable treatment option in cases with periapical lesions.

The aim of this study was to describe and evaluate the use of PRGF®-Endoret® in the treatment of defects post-extraction. 14 patients were included who required the extraction of different teeth and in 7 of them PRGF®-Endoret® was applied while in the other 7 it was not, with this being used as the control group. After 11 to 14 weeks, the bone density was measured in the internal and external perimeter as well as in the centre of the defects using the BTI-Scan program. The results showed that bone density in the internal periphery and in the centre of the implant bed was significantly higher in the group treated with PRGF®-Endoret® with respect to the control group. Bone density was also higher in the external periphery, but without significant differences. As a result we can say that PRGF®-Endoret® promotes faster bone regeneration in alveoluses post-extraction.

The application of PRGF®-Endoret® reduces inflammation and pain, accelerates the epithelisation of soft tissues and promotes bone regeneration.
The aim of this split-mouth study was to evaluate the efficacy of PRGF®-Endoret® in the regeneration of alveoluses post-extraction in impacted third molars. To this end the cytokines in the mucous tissues were analysed after the extraction with the application or not of PRGF®-Endoret®. Post-op pain and facial swelling were also assessed.

The results showed that the inflammation parameters and the regeneration process of the lesion were all significantly better in the areas treated with PRGF®-Endoret® than in the control areas. On the other hand the post-op pain and facial swelling were less in the areas treated with PRGF®-Endoret®.

In short, based on the results obtained it can be stated that PRGF®-Endoret® can be routinely used in the regeneration of impacted third molars.

This article describes a clinical case in which PRGF®-Endoret® was used to preserve the architecture of the soft tissues associated with an implant that was placed immediately after an extraction at the back of the superior maxilla. This procedure allowed a guided bone regeneration without the need to carry out vertical releasing incisions, presenting a good gingival outline in facial appearance after a single surgical phase.

In some situations, there is a lack of bone support due to atrophy, trauma or surgical resection. As dental implants can only be placed if there is enough bone to be able to adequately stabilise them, the procedures for bone augmentation are an effective therapeutic option for these kinds of situations. In fact, in patients with long-term edentulous sites, even severe bone resorptions are frequently observed (both vertical and horizontal or combined defects). As a result, the use of additional techniques for bone augmentation is essential. Some of these techniques include the use of growth factors, osteogenic distraction, guided bone regeneration, the use of re-vascularised bone grafts and techniques such as ridge expansion or expanders or Split-Crest with ultrasonics.
The aim of this study was to clinically evaluate the ridge expansion technique with ultrasonics called the Split-Crest technique, for the placement of dental implants in patients with narrow ridges. After at least 6 months after loading the implants, the state of the hard and soft tissues and the expansion achieved were evaluated, as well as the survival rate of the implants. 15 patients were included whose previous average ridge width was 4.29 mm and who received a total of 37 implants. PRGF®-Endoret® was applied during surgery to encourage tissue regeneration. The results showed that the state of the soft tissues was very good with adequate values of plaque index, bleeding and probing depth. The implant survival rate was 100 %. The average bone expansion achieved was 3.35 mm. These results showed how the Split-Crest technique with ultrasonics along with the application of PRGF®-Endoret® can be considered an effective and safe technique for bone expansion in narrow ridges.

This article rescribes a new ridge expansion technique called the two-stage Split-Crest technique indicated for patients with severely resorbed ridges (3-4 mm). It consists of an expansion carried out in 2 consecutive stages using transitional implants. The implants used as transitional implants (2.5 and 3.0 mm diameter) were replaced from 5 to 7 months after their placement with others with a larger diameter. The state of the soft tissues was good with adequate probing depth values (average value was 3.06 mm). The average bone expansion achieved after the procedure was 8.49 mm apical and 7.10 mm occlusal. There were no implant failures during the follow-up period. These preliminary results prove the predictability and safety of the two-stage Split-Crest technique and its potential use in patients with severely resorbed ridges, as well as avoiding the use of other more aggressive techniques such as bone grafts.
The new two-stage Split-Crest technique using transitional BTI implants allows an expansion of the ridge of 7 - 8 mm.
The aim of this randomised clinical test was to evaluate the effectiveness of anorganic bovine bone in ridge expansion with a titanium mesh and to investigate the effect of PRGF®-Endoret® in preventing mesh exposure, given that it is a frequent complication in these procedures. 30 patients were included on whom a total of 43 ridge expansions were carried out. In 15 of them PRGF®-Endoret® was used to cover the titanium mesh, while it was not used in the rest (control).

After 6 months of evolution, the results showed significant differences between the 2 groups regarding the complications and bone formation. In the group treated with PRGF®-Endoret® there was no mesh exposure while in the control group there was an exposure rate of 28.5%. The radiological analysis showed that bone augmentation was higher in the group with PRGF®-Endoret®. On the other hand the implant survival rate was 100% in the group with PRGF®-Endoret® and 97.3% in the control group.

The aim of this randomised clinical trial was to evaluate the use of BTI motorised ridge expanders and to compare their results with those obtained by means of the lateral ridge expansion technique. 8 bilateral patients were included on whom the technique with expanders was applied to one side while on the other the lateral technique was used. The implants were placed 6 months later. The results showed significant differences in the bone expansion achieved with both techniques (1.5 mm with the motorised expanders and 1.2 mm with lateral expansion). These results showed the effectiveness of motorised expanders for the expansion of narrow ridges. In addition, the defects treated with expanders presented less bone width contraction during the first 6 months.

The insertion of implants in the posterior region of the superior maxilla is a difficult clinical procedure. Progressive horizontal and vertical bone resorption increases the sinus cavity while the maxillary sinus floor thickness is reduced.

An absence of superior molars can even increase bone resorption, leading to the pneumatization of the sinus due to an increased activity of osteoclasts in Schneider's membrane.

These limitations can make it difficult to place an implant and can negatively affect the success of its osseointegration and the stability of the dental implants.

The most frequently applied surgical procedure to reestablish an adequate bone volume and an adequate ridge height in the posterior region of the maxilla is an augmentation of the maxillary sinus. This technique involves the modification of the sinus cavity with the aim of generating sufficient bone volume within a space that used to be part of the sinus cavity.

Sinus elevation

Clinical Research
The protocol consists of a) carrying out a complete osteotomy with surgical ultrasonics, b) filling in the sinus with a graft soaked in PRGF®-Endoret®, c) replacing the bone window and a fibrin membrane, and d) placing the implants months later.
Sinus elevation

Clinical Research

This article describes the sinus elevation technique with the use of an osteotomy with ultrasonics. This is the first job that uses surgical ultrasonics. This technique offers important advantages over a conventional osteotomy that uses diamond tool bits. In addition, it reduces the risk of perforating Schneider’s membrane. On the other hand it improves the vision and hygiene of the surgical area and provides a more conservative and controlled bone incision.

The aim of this study was to evaluate a modified sinus elevation technique with osteotomes and the immediate placement of implants and the application of PRGF®-Endoret®. A total of 14 patients were included on whom this technique was carried out and the results showed that after an average follow-up period of 36 months, none of the implants failed and marginal bone loss after 1 year of load was 0.36 mm. All the treatments were successful.


The aim of this randomised clinical trial was to evaluate whether PRGF®-Endoret® improves the effectiveness of inorganic bovine bone in the sinus elevation technique. 87 patients were included on whom a total of 144 sinus elevations were carried out using biomaterial alone or in combination with PRGF®-Endoret®. A total of 286 implants were placed in the patients, who were monitored for 24 months. The results showed that the survival rate was higher in the implants placed using biomaterial + PRGF®-Endoret®. It should be noted that in patients with residual ridges of less that 4 mm, the implant survival rate was significantly higher in the areas treated with PRGF®-Endoret® (98.2% vs 90.7%). The histological and histomorphometric analysis revealed that the bone augmentation was significantly greater in the areas treated with PRGF®-Endoret®. These results showed that PRGF®-Endoret® can improve the osteoconductive properties of the biomaterial increasing the volume of new bone formed.

Sinus elevation

Clinical Research

The aim of this study was to describe and evaluate the lateral sinus elevation technique with the application of PRGF®-Endoret®. 18 patients were included who received a total of 43 implants. All of them presented a residual bone height of 1-3 mm. The technique consisted of carrying out a vestibular osteotomy with ultrasonics, separating the window created and keeping it submerged in PRGF®-Endoret®. Once the elevation is carried out the window is replaced in its anatomical location and covered with autologous fibrin. After 6 months the samples of bone taken from the sinuses were evaluated. The results showed that after an average follow-up period of 13 months, the implant survival rate was 100%. These results showed that the lateral sinus elevation technique using PRGF®-Endoret® can be considered a safe, effective and predictable technique.
The aim of this study was to evaluate the potential effect of PRGF®-Endoret® in the lateral approach for sinus elevation. 5 patients were included who required bilateral sinus elevations with a residual bone height of 1-3 mm. On one side PRGF®-Endoret® was used along with inorganic bovine bone, while only biomaterial was used on the other side. The use of PRGF®-Endoret® doubled the volume of the graft thanks to the action of the fibrin. Post-op pain and inflammation were greater on the control side (without PRGF®-Endoret®). The areas treated with PRGF®-Endoret® presented a larger amount of new vital bone than those without. The immunohistochemistry of the biopsies revealed that the number of blood vessels per square millimetre of connective tissue was 116 vessels as opposed to 7 in the control areas. These results showed the therapeutic potential of PRGF®-Endoret® for reducing inflammation, increasing new bone formed and generating blood vessels in these sinus elevation procedures.

Bisphosphonate-related osteonecrosis of the jaw

Clinical Research

Bisphosphonates are a group of drugs that reduce the rate of bone turnover, mainly through the inhibition of the action of osteoclasts, and they are administered both orally and intravenously in patients with oncological or rheumatic treatments. These drugs show calcium affinity and their mechanism of action at a cellular level includes the inhibition of the vascular endothelial growth factor (VEGF).

Around the year 2003 the first cases of exposed bone that would not heal in the maxillofacial region in patients treated with intravenous bisphosphonates were reported, meaning that this pathology was associated with the administration of bisphosphonates and was identified as bisphosphonate-related osteonecrosis of the jaw (BRONJ). The accumulated incidence of BRONJ has been estimated within a range of 8 to 12%, for IV administration and 0.7/100,000 people/year for oral administration.

To date, the treatments available to prevent or treat BRONJ are very limited and the results obtained are not conclusive. Recently, the use of PRGF®-Endoret® has been proposed as part of a preventive and therapeutic approach. The hypothesis of the use of this autologous technology is based on the potential effects of the growth factors released in the osteoclasts and on angiogenesis.
This article describes the clinical case of a patient affected by BRONJ after being treated for several years with zoledronic acid (IV) and after a tooth extraction. Their symptomatology includes severe pain and hemimandibular paresthesia due to affectation of the dental nerve. The treatment consisted of surgical resection of the necrotic bone area combined with the application of PRGF®-Endoret®.

One month after surgery, total closure of the ulcerous lesion in the mucous membrane was observed without the presence of necrotic bone. 6 months later, a significant improvement of the pain and paresthesia was observed. After a year, the patient had totally recovered sensitivity and the absence of necrotic bone was confirmed.

These clinical results support the use of PRGF®-Endoret® as an adjuvant treatment for patients with BRONJ.

The aim of this study was to describe and evaluate the use of PRGF®-Endoret® within the surgical tooth extraction protocol for patients in treatments with biphosphonate drugs and its role in the prevention of biphosphonate-related osteonecrosis of the jaw (BRONJ). A total of 64 patients were included on whom a total of 220 extractions were carried out and in all of them PRGF®-Endoret® was applied to cover the defect and to encourage a correct regeneration of tissues. The patients were monitored for at least 4 months. Bisphosphonate-related osteonecrosis of the jaw only occurred in 5 post-extraction sites (2.27%). In the mandible, the cases of BRONJ were more frequent. The results of this study show that PRGF®-Endoret® is a possible alternative to prevent these lesions in patients in treatment with biphosphonates who have had dental extractions.

The aim of this study of case and control groups was to determine the role of PRGF®-Endoret® in the prevention of bisphosphonate-related osteonecrosis of the jaw in patients who took IV biphosphonates and who had dental extractions. The study included 100 patients, of whom 50 received PRGF®-Endoret® after the extraction while the rest did not receive PRGF®-Endoret® (control group). The patients were monitored for a period ranging between 24 and 60 months, carrying out annual checkups and scans. BRONJ was diagnosed in 2 patients and both were from the control group. Despite the small number of patients, these results may suggest that treatment of extractions with PRGF®-Endoret® may reduce the risk of developing BRONJ by these patients at risk receiving treatment with IV biphosphonates.

BTI implants

Clinical Research

The range of BTI implants presents a series of special and differential features. All of them have a surface treatment that gives them excellent humectability, thus obtaining a nanometric bioactive surface ideal in combination with PRGF®-Endoret® to shorten their osseointegration periods. On the other hand, their surface provides an excellent titanium-bone interface and maximum bone apposition is achieved with an increase of BIC (bone-implant contact). Its self-tapping apex with excellent advancing capacity and small apical surface avoids compressions and facilitates its directional control and placement in narrow ridges. Within the range of BTI implants, we should highlight the family of short (≤ 8.5 mm) and extra-short (≤ 6.5 mm) implants that have proven their high long-term predictability.
This retrospective study with BTI implants was published in the journal with the greatest scientific impact in the field of dentistry. Its aim was to evaluate the long-term survival of BTI implants and to identify the possible risk factors associated with implant failures. A total of 5787 BTI implants of different diameters and lengths were included in the study. The results showed that the implant survival rate was 99.2%, 96.4% and 96.0% for the analysis based on the implant, on the surgery and on the patient, respectively. The risk factors that could be related to a higher implant failure rate were two-stage surgery and the use of special surgery-related techniques. These results attest to the predictability and safety of BTI's range of implants.

Immediate load

This study was carried out with the aim of describing the immediately loaded dental implant insertion technique and to evaluate the long-term survival, as well as the possible risk factors related to its failure. A total of 1139 implants were included and a survival rate of 99.3%, 96.8% and 96.9% was observed for the analysis based on the implant, on the surgery and on the patient, respectively. Only 5 of the implants failed during the follow-up period and no failure-related risk factors were found. These results showed the predictability of the immediate load technique described provided it is used with appropriate insertion torques and following strict clinical protocols.

Several years after starting the clinical use of short implants, the decision was made to carry out this study, the aim of which was to evaluate the long-term survival of short BTI implants (≤ 8.5 mm) in posterior areas of the superior maxilla and the mandible. A total of 532 implants placed in 293 patients were included. The results showed a survival rate of 99.2% and 98.7% for the analysis based on the implant and on the patient, respectively. Two of the implants failed due to different causes after an average follow-up period of 31 months. No risk factors related to the failure of the short implants could be identified. These results showed the high predictability of the use of short implants in posterior areas.

The aim of these studies was to evaluate the long-term survival (up to 8 years of follow-up) of short and extra-short BTI implants (≤ 8.5 mm) in posterior areas of the superior maxilla and the mandible. In the first of them, a total of 1287 short implants placed in 661 patients were included. The results showed a survival rate of 99.3% and 98.8% for the analysis based on the implant and on the patient, respectively. Nine of the implants failed due to different causes. No risk factors related to the failure of the short implants could be identified.

In the second study the extra-short implants (≤6.5) were also studied separately, showing survival rates of 97.9% and 97.1% for the implants and patients, respectively.

These results showed that treatment with short and extra-short implants can be considered a safe and predictable technique if used following strict clinical protocols.
Short and extra-short implants allow rehabilitations in atrophic ridges without having to resort to more aggressive techniques such as bone grafts.
This study was carried out with the aim of evaluating the influence of an unfavourable crown/implant ratio (≥1) and other variables of the implant, be they surgical, prosthetic or biomechanical, on Marginal Bone Loss and on the survival of short implants in posterior areas. A total of 128 implants placed in 63 patients were evaluated. The average follow-up period was 22 months. The average C/I ratio of the implants was 1.82. In 86 of them it was <2 and in 42 implants ≥2. The marginal bone loss observed was 0.35 mm during the first year post-load and 0.45 mm after the first year post-load. The implant and prosthesis survival rate was 100 %. The unfavourable C/I ratio did not show any relationship with the marginal bone loss of the implants. Of the remaining variables studied, the only one that showed a negative influence was the use of cantilevers in prosthetic rehabilitations.

The aim of this study was to evaluate the influence of a very unfavourable crown/implant ratio (≥2) and other variables, be they surgical, prosthetic or biomechanical, on Marginal Bone Loss and on the survival of short implants in posterior areas. A total of 42 implants placed in 28 patients were evaluated. The average follow-up period was 28 months. The average C/I ratio of the implants was 2.30. The marginal bone loss observed was 0.38 mm and 0.24 mm mesial and distal, respectively. The implant and prosthesis survival rate was 100 %. The very unfavourable C/I ratio did not show any relationship with the marginal bone loss of the short implants in posterior areas. No relationship was found between the rest of the variables studied and marginal bone loss.

Anitua E, Begoña L, Piñas L, Orive, G. Short and extra-short implants with a very unfavorable crown-to-implant ratio (≥2) in posterior regions. Influence on marginal bone loss and survival rate. 2012.
This study was carried out to evaluate the long-term survival and clinical effectiveness of narrow-diameter (2.5 and 3.0 mm) BTI Tiny implants in patients with an insufficient ridge (2.5 to 4.0 mm) to allow the placement of standard-diameter implants. 51 patients were included who received a total of 89 implants. The results showed a survival rate of 98.9% and 98.0% for the analysis based on the implant and on the patient, respectively. Only one implant failed 12 months after its placement. Average bone loss after 2 years of implant load was 1.26 mm. These results showed that 2.5 and 3.0 mm Tiny implants can be used effectively and safely for the treatment of narrow and severely resorbed ridges.
“The many clinical studies carried out with BTI implants prove their versatility, safety and predictability”
This article describes for the first time the concept of “de-osseointegration” of implants. For this purpose a new technique has been developed that uses the BTI Explantation Kit, which facilitates an easy and atraumatic explantation while keeping the walls of the alveolar bed intact to allow the placement of a new implant. In this study a total of 58 explantation cases of different implants were included using the BTI Explantation Kit. The removal torque varied between 80 and 200 Ncm. In 20 cases a new implant was placed. This article shows how the possibility of explanting dental implants atraumatically opens new doors in oral implantology.
This study was carried out with the aim of describing and evaluating the new technique for the atraumatic explantation of implants. This new technique facilitates a fast explantation, keeping the alveolar bed walls intact and at the same time facilitating the insertion of a new implant during the same surgical operation. In this study 91 implants explanted from a total of 42 patients were included. The removal torques varied between 80 and 200 Ncm. In those cases where the implant removal torque exceeded 200 Ncm, 2-3 mm incisions were carried out with a set of atraumatic trephines to avoid excessively high torques.

These results showed how the possibility of explanting implants atraumatically can be considered a viable alternative to replace failed implants.

The aim of this randomised clinical trial was to assess the need or not to administer an antibiotic prophylaxis with 2 g of oral amoxicillin one hour before the single dental implant insertion surgery to avoid post-op infections. 12 private centres which recruited a total of 105 patients took part. 52 patients received amoxicillin and 53 received a placebo.

After 6 months, there were 6 infections and 2 implant failures in each group. No statistically significant differences were found for post-op infections, adverse events or implant failures between both groups. Observing the results of this study, antibiotic prophylaxis for single implants may not be necessary.
In this article, the aim was to describe and compare with the traditional drilling system a low-revolution drilling system (50-100 r.p.m) that allows surgeons to obtain live autologous bone that can be associated with PRGF®-Endoret® to be used in bone grafts. Bone particles using both conventional techniques and the new low-revolution drilling system were collected and analysed under a microscope. The microscopic examination showed that the bone structure and the presence of live cells was preserved in all the samples collected with low-revolution drilling while these qualities were not maintained with conventional drilling. This new drilling technique can reduce damage to the host tissue and can be used to obtain a mass of live bone ideal for carrying out bone grafts associated with PRGF®-Endoret®.

Aging is a multi-factorial process that is characterised by a progressive reduction of the functional capacity of all the body’s tissues and organs, with the consequent loss of ability to adjust to environmental stimuli. It is a known fact that skin aging is produced by cellular or intercellular matrix degradation, reduced vascularisation, a dysfunction of skin annexes, fat atrophy and muscular atrophy or relaxation. These phenomena are fundamentally influenced by the inexorable passage of time and genetics, in addition to other factors such as sun exposure, diseases, nutrition, toxic habits, etc.

The most evident signs of aging are wrinkles, dyschromias and ptosis, and other less evident ones, such as the texture, feel, colour, shine and brightness, which globally determine the final appearance of the skin.

Today, and due to social pressure, increasing importance is given to our physical appearance, where it is considered acceptable and even necessary in more and more circles to struggle to maintain a youthful and healthy appearance. This growing aesthetic awareness means that the interest in developing new products to help us improve the appearance of our skin has increased.

Facial regeneration
“PRGF®-Endoret® represents the first biological therapy for personalised medicine that has proved its effectiveness in facial regeneration and anti-aging.”
In this randomised clinical trial the effectiveness and safety of PRGF®-Endoret® was evaluated in the cutaneous regeneration of aged skin, comparing it with hyaluronic acid. A total of 100 patients were included with evident external signs of aged skin and were randomly assigned treatment with PRGF®-Endoret® or with hyaluronic acid. The level of skin moisturisation, cutaneous concentration of fat and skin pH, the level of severity of the wrinkle and patient satisfaction were evaluated. The results showed that in both follow-up visits the skin moisturisation and pH values as well as the satisfaction rate were significantly higher in the group treated with PRGF®-Endoret® (p<0.05) than in the control group. On the other hand, the fat index drop after 3 months was significantly lower in both groups with respect to the baseline visit. These results support the application of PRGF®-Endoret® in the treatment of age-related skin aging, obtaining excellent mid and long-term results after its application.

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Publications

Traumatology, orthopaedic surgery and sports medicine

Revision articles


Preclinical Research

• Anitua E, Andía I, Sanchez M, Azofra J, del Mar Zalduendo M, de la Fuente M, Nurden P, Nurden AT. Autologous preparations rich in growth factors


Critical Research

- Sanchez M, Anitua E, Andia I. Application of Autologous Growth Factors on Skeletal Muscle Healing. 2nd World Congress on Regenerative Medicine, May 18-20, 2005, Leipzig, Germany
PRGF®-Endoret® has been a pioneer proving its effectiveness in the treatment of osteoarthritis and tendinopathies.
Publications

Dermatology


Preclinical Research


Clinical Research
